BIOGRAPHICAL SKETCH

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NAME: Lee, Charles

eRA COMMONS USER NAME (credential, e.g., agency login): CL1234

POSITION TITLE: Scientific Director and Professor, The Jackson Laboratory for Genomic Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Alberta, Alberta, Canada	B.S.	06/1990	Genetics
University of Alberta, Alberta, Canada	M.Sc.	06/1993	Experimental Pathology
University of Alberta, Alberta, Canada	Ph.D.	06/1996	Medical Sciences
Cambridge University, Cambridge, UK	Postdoc	06/1998	Molecular Cytogenetics
Harvard Medical School, Boston, MA USA	Postdoc	06/2001	Clinical Cytogenetics

A. Personal Statement

My career in human genomics has spanned over 15 years and began with a simple premise of understanding more about the human genome and how seemingly insignificant variations in DNA could give rise to different traits and phenotypes. One of our notable discoveries came by way of the first description of widespread structural variants (SVs) – in the form of copy number variants (CNVs) – in the human genome. We demonstrated that large genomic changes (i.e., gains or losses of thousands-to-millions of nucleotides) are common, pervasive, and often hold important implications for understanding the genetic basis of human health and disease. We subsequently developed two human CNV maps that serve the basis of our understanding of common structural human genomic variants and are routinely used for differentiating pathogenic genomic imbalances from common variants in clinical genomic tests. This discovery was acknowledged as the breakthrough of the year by *Science Magazine* in 2007 as well as Thompson Reuter's selection of its 2012 Citation Laureates.

From 2000-2012, I led several research, educational and clinical genetics programs, in my capacity as Director of the Dana-Farber/Harvard Cancer Center Cytogenetics Core, Director of the Molecular Genetics Research Unit at Brigham and Women's Hospital, and appointments at Harvard Medical School and the Broad Institute. In 2013, I became the Scientific Director of The Jackson Laboratory for Genomic Medicine, where I have been able to develop and lead a team of world-renowned investigators with the collective goal of translating scientific discoveries into novel diagnostic tests and individualized treatments. At the Jackson Laboratory for Genomic Medicine, my research program encompasses three areas: 1) SVs in the human genome, 2) clinical genomic diagnostics and 3) cancer genetics and biomarkers. The current proposal will benefit from my group's expertise in leading large-scale SV projects and developing computational methods for SV discovery, as demonstrated by our participation in the 1000 Genomes Project.

B. Positions and Honors

Positions and Employment

1993	Invited Research Trainee, Johns Hopkins School of Medicine, Baltimore, MD
2000-2006	Assistant Director, Harvard Cancer Center Cytogenetics Core, Boston, MA
2001-2003	Instructor in Pathology, Harvard Medical School, Boston, MA
2001-2008	Associate Clinical Cytogeneticist, Brigham and Women's Hospital, Boston, MA
2003-2008	Assistant Professor of Pathology, Harvard Medical School, Boston, MA
2006-2013	Director, Harvard Cancer Center Cytogenetics Core, Boston, MA
2006-2013	Associate Member, Broad Institute of Harvard and MIT, Boston, MA

2008-2011 Associate Professor of Pathology, Harvard Medical School, Boston, MA
2008-2013 Clinical Cytogeneticist, Brigham and Women's Hospital, Boston, MA
2009-2013 Director, Molecular Genetics Research Unit, Brigham and Women's Hospital, Boston, MA
2013-Present Scientific Director and Professor, The Jackson Laboratory for Genomic Medicine, Farmington, CT

Awards and Honors

1994 75th Anniversary Faculty of Medicine Scholarship, University of Alberta, Canada
1994-1996 PhD Studentship, Alberta Heritage Foundation for Medical Research, Canada
1996 MRC Postdoctoral Fellowship, Medical Research Council of Canada
1996-1998 NSERC Postdoctoral Fellowship, Natural Sciences and Engineering Research Council of Canada
2002 Stanley L. Robbins Research Award, Department of Pathology, Brigham and Women's Hospital, Boston, MA
2008 Ho-Am Prize in Medicine, Ho Am Foundation, Seoul, South Korea
2008 C. Thomas Caskey Award, University of South Carolina, SC
2010 George W. Brumley, Jr., M.D. Memorial Award, Duke University, Durham, NC
2012 Chen Global Investigator Award, Human Genome Organization (HUGO)
2012 Fellow, American Association for the Advancement of Science (AAAS)
2012 Vandenberghe Visiting Chair, Center for Human Genetics, Catholic University of Leuven, Belgium
2013-2015 Distinguished Visiting Professor, Seoul National University School of Medicine, Korea
2014 Citation Laureate, Thompson Reuter, USA
2015-Present Distinguished EWHA University Visiting Professor, EWHA Womans University, Korea

Other Professional Activities

2002-Present Diplomate, American Board of Medical Genetics
2004 Ad hoc reviewer, Genome Canada Grant Competition
2005 Ad hoc reviewer, NSF Peer Review Committee
2006-2008 Member, NIH/ NHGRI Structural Variation Steering Committee
2007-2010 Member, American Society of Human Genetics Program Committee
2008-2012 Faculty, Program in Quantitative Genomics at Harvard School of Public Health
2008-2012 Scientific Advisory Board, Yale Center for Excellence in Genome Sciences
2008-Present Co-chair, 1000 genomes project (www.1000genomes.org) - SV Analysis Group
2009 Chair, NHGRI Cytogenetics Core Advisory Board
2009-2011 Associate Editor, *American Journal of Human Genetics*
2009-2012 Director, Cancer Cytogenomics Microarray Consortium Board of Directors
2015-Present Associate Editor, *Genomic Medicine*
2015-Present Editorial Board, *Human Genomics*

C. Contribution to Science

1. **Structural and Copy Number Variation in the Human Genome and the genomes of model organisms.** Our research in human structural genomic variation aims to accurately identify and characterize deletions, duplications and balanced chromosomal rearrangements in the genomes of humans and model organisms and understand the biological implications of these variants. We originally described the widespread presence of structural genomic variants in the human genome and have extended our studies to specific world populations. Over the past five years, we have led the structural variation group of the 1000 Genomes Project (an international collaboration aimed at identifying and cataloging all genetic variants occurring at a frequency of at least 1% in 26 world populations, http://www.1000genomes.org/) and have developed methods for identifying human structural genomic variants at higher resolution from whole genome sequence analyses.
   a. Iafrate AJ, Feuk L, Rivera MN, Listewnik ML, Donahoe PK, Qi Y, Scherer SW, **Lee C**. Detection of large-scale variation in the human genome. *Nature Genetics*. 2004; 36(9):949-51. PMID: 15286789
   b. Park HS, Kim JI, Ju YS, Gokcumen O, Mills, RE, … , Darvishi K, Yang SJ, Yang KS, Kim HT, Hurles ME, Scherer SW, Carter NP, Tyler-Smith C, Seo JS, **Lee C**. Absolute quantification of common Asian copy number variants (CNVs) using an integrated approach of high resolution array CGH and massively parallel DNA sequencing. *Nat Genet*. 2010; 42: 400-5. PMCID: PMC3329635

c. Mills RE, Walter K, Stewart C, Handsaker RE, Chen K, Alkan C, … , Eichler EE*, Gerstein MB*, Hurles ME*, **Lee C***, McCarroll SA*, Korbel JO*. Mapping copy number variation by population-scale genome sequencing. *Nature*. 2011; 470(7332):59-65. PMCID: PMC3077050 **co-senior author*

d. Sudmant PH, Rausch T, Gardner EJ, Handsaker RE, Abyzov A, … , Mills RE*, Gerstein M*, Bashir A*, Stegle O*, Devine SE*, **Lee C***, Eichler EE*, Korbel JO*. An integrated map of structural variation in 2,504 human genomes. *Nature*. 2015 Oct 1;526(7571):75-81.**co-senior author* PMCID: PMC4617611 **co-senior author*

2. **Structural and Copy Number Variation in the genomes of model organisms.** Understanding the biological implications of specific structural genomic variants requires the accurate identification and genotyping of these variants in cell lines and model organisms. To optimize genomic studies in model organisms and more accurately understand the contributions of specific variants to human diseases, we have developed the first structural genomic maps for several non-human genomes, including the zebrafish, the Chimpanzee, and the Rhesus Macaque. We have further shown that most of these structural variants lie outside of genes but yet can dramatically influence cellular transcriptional profiles.
   a. Perry GH, Tchinda J, McGrath SD, Zhang J, Picker SR, Caceres AM, Iafrate AJ, Tyler-Smith C, Scherer SW, Eichler EE, Stone AC, **Lee C**. Hotspots for copy number variation in chimpanzees and humans. *Proc Natl Acad Sci USA*. 2006; 103: 8006-11. PMCID: PMC1472420
   b. Lee AS, Gutierrez-Arcelus M, Perry GH, Palacios R, Vallender EJ, Johnson WE, Miller GM, Korbel JO, **Lee C.** Analysis of copy number variation in the rhesus macaque genome identified candidate loci for evolutionary and human disease studies. *Hum Mol Genet*. 2008; 17: 1127-36.
   c. Brown, KH, Dobrinski KP, Lee AS, Gokcumen O, Mills RE, Shi X, Chong WW, Chen JY, Yoo P, David S, Peterson SM, Raj T, Choy KW, Stranger B, Williamson RE, Zon LI, Freeman JL, **Lee C**. Extensive genetic diversity and sub-structuring among zebrafish strains revealed through copy number variant analysis. *Proc Natl Acad Sci USA*. 2012; 109: 529-534. PMCID: PMC3258620
   d. Iskow RC, Gokcumen O, Abyzov A, Malukiewicz J, Zhu Q, Sukumar AT, Pai AA, Mills RE, Habegger L, Cusanovich DA, Rubel MA, Perry GH, Gerstein M, Stone AC, Gilad Y, **Lee C**. Regulatory element copy number differences shape primate expression profiles. *Proc Natl Acad Sci USA*. 2012; 109: 12656-61.

3. **Clinical Genomic Diagnostics.** Combining our laboratory's interest in advanced molecular technologies, the search for new biomarkers and clinical expertise as a board-certified clinical cytogeneticist, our laboratory is well poised to develop new clinical genomic diagnostic tests. Some of our newly developed assays include (1) the *TMPRSS2* and *ETS* transcription factor in aggressive prostate cancer, and (2) *MET* amplification in gefitinib-resistance non small cell lung carcinoma.
   a. **Lee C**, Gisselsson D, Jin C, Nordgren A, Ferguson DO, Blennow E, Fletcher JA, Morton CC. Limitations of chromosome classification by multicolor karyotyping. *Am J Hum Genet*. 2001; 68: 1043-7.
   b. **Lee C**, Iafrate AJ, Brothman AR. Copy number variations and clinical cytogenetic diagnosis of constitutional disorders. *Nat Genet*. 2007; 39: S48-S54.
   c. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM Mehra R, Sun X-W, Varambally S, Cao X, Tchinda J, Kuefer R, **Lee C**, Montie JE, Shah RB, Pienta KJ, Rubin MA, Chinnaiyan AM. Recurrent fusion of *TMPRSS2* and ETS transcription factor genes in prostate cancer. *Science.* 2005; 310: 644-8.
   d. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale C-M, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, **Lee C**, Johnson BE, Cantley LC, Janne PA. *MET* amplification leads to gefitinib resistance via ERBB3 in *EGFR* mutant lung cancer. *Science*. 2007; 316: 1039-43.

4. **Cancer Genomics.** Our research has been focused on the study of human cancer genome sequences and structures to provide insights into cancer biology, diagnosis and therapy. Thus, we have undertaken a number of studies directed towards molecular cytogenetics of cancer. More recently, we have initiated a large-scale project using patient-derived xenograft (PDX) tumor models established in NSG (Nod-SCID-IL2RKO) immunodeficient mice bearing the human immune system. This serves as a personalized animal model of a patient's tumor, which can be used in both co-clinical trials for drug efficacy as well as the development of databases for genomic profiles and clinical outcomes.
   a. Garraway LA, Widlund HR, Rubin MA, Berger AJ, Sridhar R, Chen F, Beroukhim R, Getz G, Milner DA, Granter SR, Du J, **Lee C**, Wagner SN, Li C, Golub TR, Rimm DL, Meyerson M, Fisher DE, Sellers WR. Integrative genomic analysis identify *MITF* as a lineage survival oncogene amplified in malignant melanoma. *Nature*. 2005; 436:117-22.

b. Demichelis F, Setlur SR, Banerjee S, Chakravarty D, Chen JY, Chen CX, Huang J, Beltran H, Oldridge DA, Kitabayashi N, Stenzel B, Schaefer G, Horinger W, Bektic J, Chinnaiyan AM, Goldenberg S, Siddiqui J, Regan M, Kearney M, Soong TD, Rickman DS, Elemento O, Wei JT, Scherr DS, Sanda MA, Bartsch G, Klocker H*, Rubin MA*, **Lee C*.** Identification of functionally active, low frequency copy number variants at 15q21.3 and 12q21.31 associated with prostate cancer risk. *PNAS*. 2012; 109(17):6686-91. PMCID: PMC3340033 **co-senior author*
c. Chen Z, Cheng K, Walton Z, Wang Y, Ebi H, … , **Lee C**, … , Engelman JA, Wong KK. A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. *Nature*. 2012; 483(7391):613-7. PMCID: PMC3385933
d. Yang L, Luquette LJ, Gehlenborg N, Xi R, Haseley PS, Hsieh C-H, Zhang C, Ren X, Protopopov A, Chin L, Kucherlapati R, **Lee C***, Park PJ*. Diverse mechanisms of somatic structural variations in human cancer genomes. *Cell*. 2013; 153(4):919-29. PMCID: PMC3704973 **co-senior author*

A complete list of published work can be found in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41142830/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

U41 HG007497 Lee (PI) 08/01/13-06/30/17
NIH/NHGRI
An integrative analysis of structural variation for the 1000 Genomes Project
The major goal of this project is to develop and assess new methods for accurately identifying structural genomic variants in next generation DNA sequencing datasets.
Role: Program Director

U41 HG006834 Ledbetter, Martin, Mitchell, Nussbaum, Rehm (PI) 10/01/13-07/31/16
NIH/NHGRI
A Unified Clinical Genomics Database
The goal of this project is to collect and organize genome-wide structural and sequence-level variation data from many sources into a free and publically accessible environment and enable expert curation of that data for use in improving healthcare and biomedical research.
Role: Consortium Principal Investigator

Completed Research Support

P01 HD068250 Donahoe (PI) 07/01/11-06/30/16
NIH/NICHD
Gene Mutation and rescue in Congenital Diaphragmatic Hernia
The major goal of this project is to explore and compare the impact of using WGS in clinical conditions.
Role: Principal Investigator of Project 2

R01 A1089246 Simon (PI) 06/01/10-05/31/15
NIH/NIAID
Genomic Determinants of Intrinsic Antiviral host Defenses
The major goal of this project was to identify copy number variants associated with increased susceptibility to infectious disease.
Role: Co-Investigator

U01 HG005725 Lee (PD) 08/18/10 – 05/31/13
NIH/NHGRI
Analysis of Patterns of Structural Variation in the 1000 Genomes Data Set
The major goal of this project is to characterize structural genomic variation in the 1000 Genomes next generation whole-genome DNA sequencing datasets and bioinformatically predict function.
Role: Program Director